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(54) Title: CHIRAL INTERMEDIATE AND PROCESS FOR THE PRODUCTION THEREOF

(57) Abstract: The present invention relates to a new chiral intermediate, process for the production thereof, and process for the production of a HMG-CoA reductase inhibitor using the chiral intermediate.

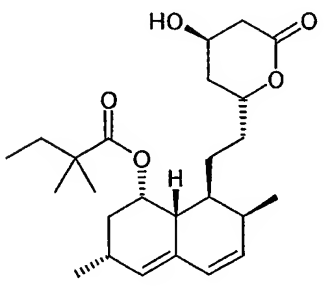
Chiral intermediate and process for the production thereof

Technical Field

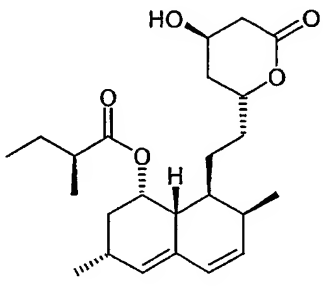
The present invention relates to new chiral intermediates, process for the production thereof, and process for the production of HMG-CoA reductase inhibitors using the same. More specifically, the present invention relates to new chiral intermediates which can be used for the preparation of HMG-CoA reductase inhibitors, a process for simply producing them under mild conditions with high yields, and a process for the production of HMG-CoA reductase inhibitors using the same.

Background Art

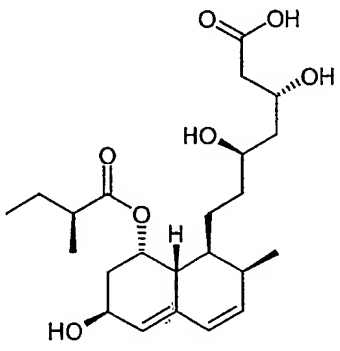
Drugs having the effect of suppressing the biosynthesis of cholesterol by inhibiting the activity of HMG-CoA(3-hydroxy-3-methyl-glutaryl coenzyme A) reductase are normally called "statin." The first generation of the statin includes simvastatin, lovastatin, and pravastatin, which are fermentation products, and the second generation of the statin includes atovastatin, fluvastatin, rosuvastatin, and pitavastain, which are synthetic drugs. The chemical structures of the main statins are as follows:



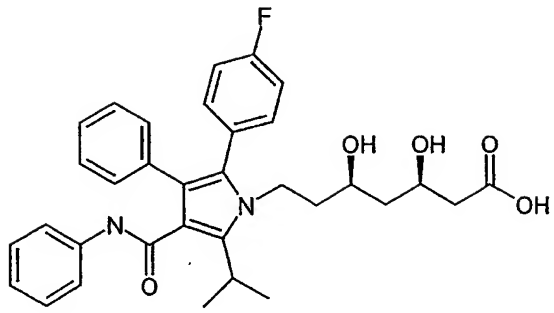
Simvastatin



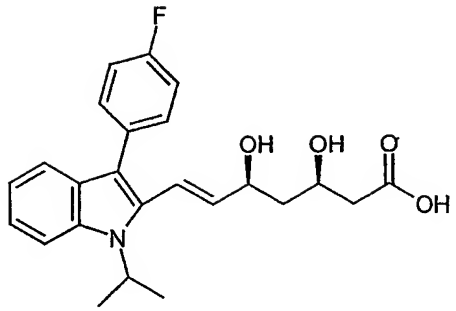
Lovastatin



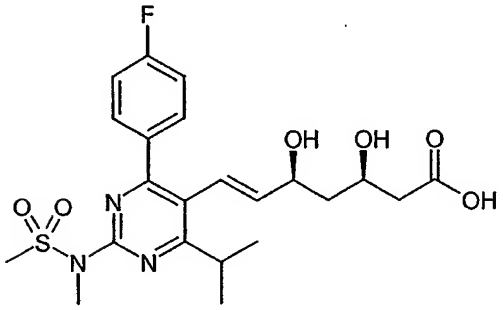
Pravastatin



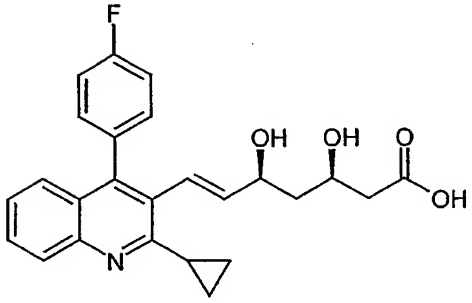
Atovastatin



Fluvastatin



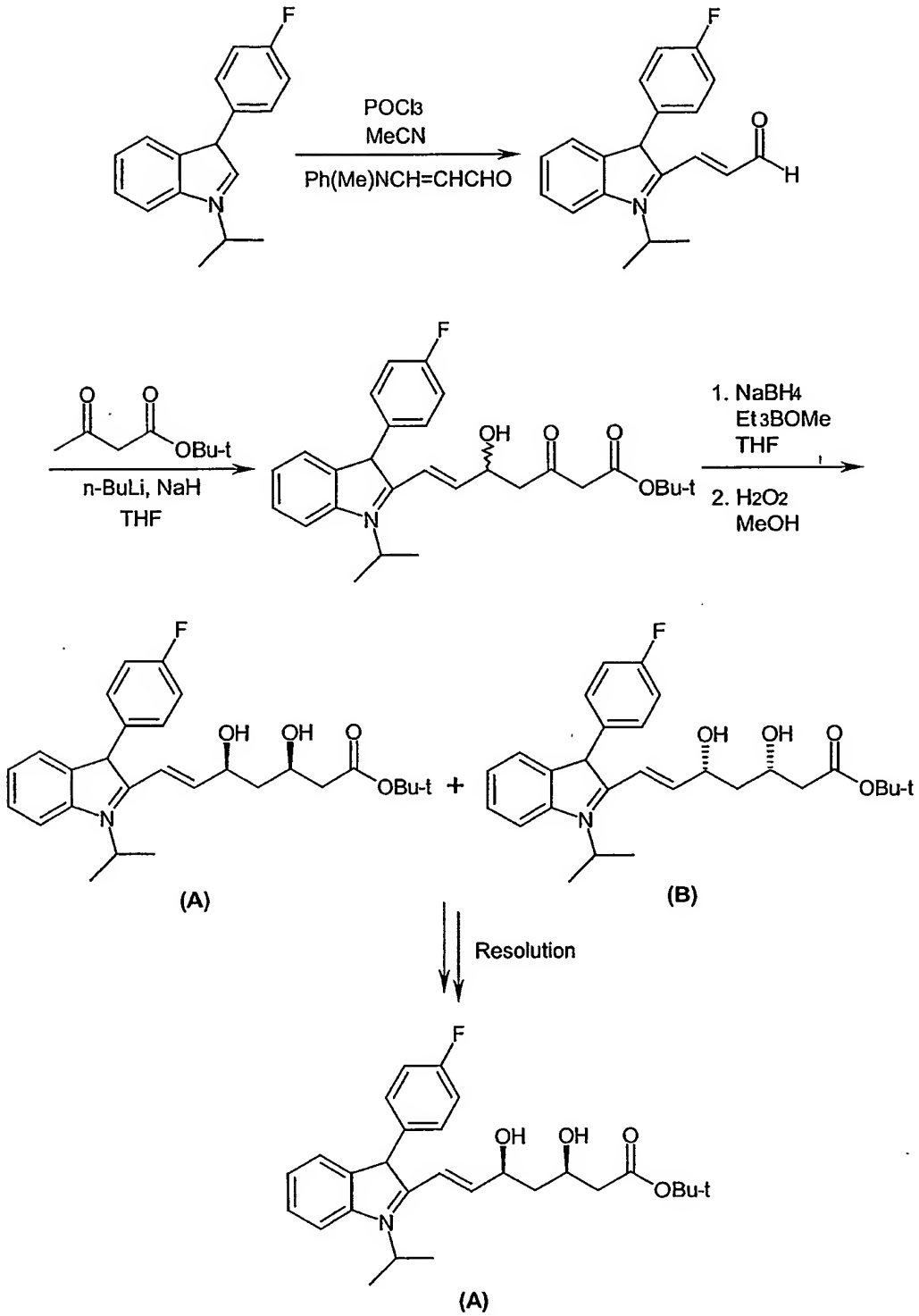
Rosuvastatin



Pitavastatin

Since all of the above compounds have optical activity, the prior processes for the production thereof used the method of preparing two racemates followed by separating them, and the method of using chiral intermediates.

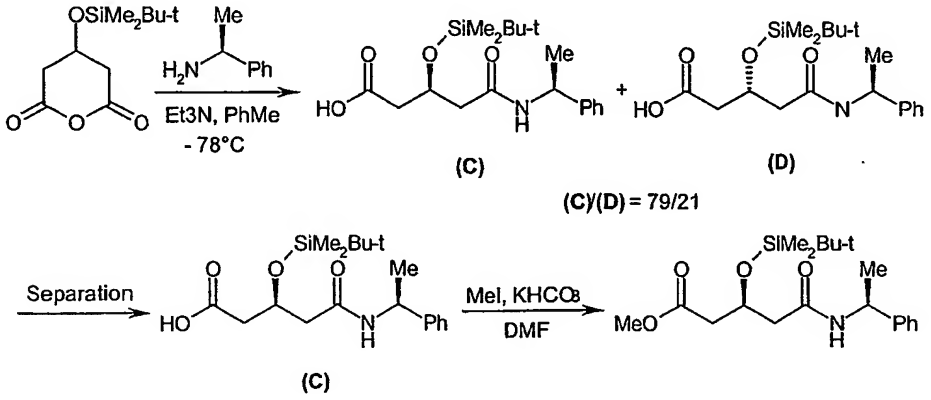
U.S. Patent No. 5,354,772 discloses a process for the production of fluvastatin, which used the method of preparing racemates and then separating them as shown in the following reaction scheme.

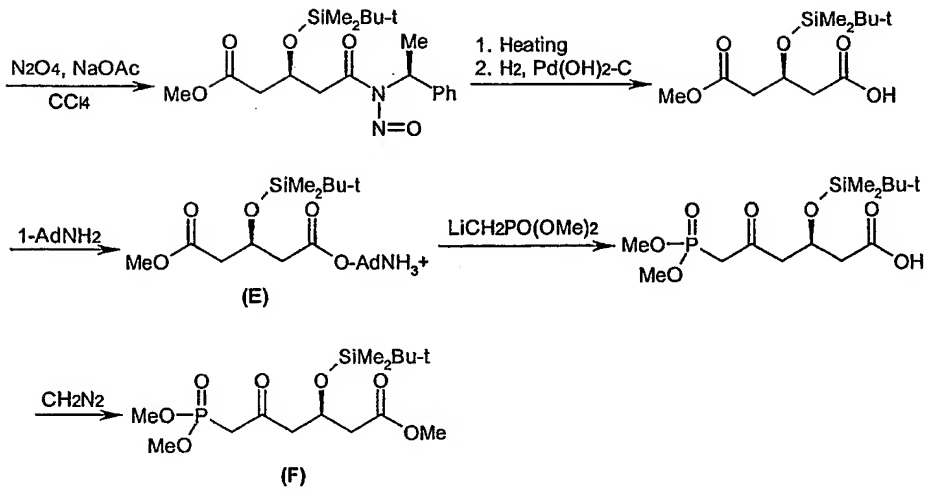

F
POCl3
MeCN
Ph(Me)NCH=CHCHO
O
H
N
OBu-t
n-BuLi, NaH
THF
OH
1. NaBH4
Et3BOMe
THF
2. H2O2
MeOH
(A)
(B)
Resolution

According to the above process, the trans-cinnamyl aldehyde was first prepared, the beta-ketoester which had been converted to a di-anion with at least two equivalents of base was introduced to the trans-cinnamyl aldehyde, and then the selective reduction reaction was carried out to obtain two chirally different syn-1,3-diols (A) and (B), which were separated by chemical, enzymatic, or chromatographic method.

However, the above process had problems as follows. Firstly, since complicated resolution procedures were needed for the achievement of desired optical purity, particularly more than 98% of optical purity from the racemates wherein compounds (A) and (B) are mixed in the ratio of 50 to 50, the yield decreased to below 50%, which increased the production costs. Secondly, the undesired isomer remaining in the product acted as an impurity to deteriorate the quality of the product.

Therefore, the method of using chiral intermediates has been variously studied [Heathcock, C.H., *J. Am. Chem. Soc.*, 1985, 107, 3731, U.S. Patent No. 5,849,749, Karanewsky D. S., *J. Org. Chem.*, 1991, 56, 3744, U.S. Patent No. 5,354,879]. The most commonly used method was that of Bristol-Myers Squibb, which used the intermediate of formula (F) prepared as shown in the following reaction scheme [*J. Org. Chem.*, 1991, 56, 3744].





However, the above method had the following problems. Firstly, an expensive chiral resolving agent such as S-1-phenylethylamine must be used, and diastereomers were obtained at most in the ratio of 79:21, although the reaction was carried out at the low temperature of –78°C. Therefore, the desired isomer should be isolated from the mixture, which reduced the yield by at least 20%. Also, the undesired isomer should be recovered and discarded.

Secondly, dangerous reactions such as N_2O_4 oxidation reaction and high-pressure hydrogenation reaction should be carried out to cleave the amine group of the resolving agent.

Thirdly, since an expensive palladium catalyst must be used during the reduction reaction with hydrogen, the method was economically disadvantageous, and the heavy metal could remain in the final product to deteriorate the quality of the product.

Fourthly, since at least 1.0 equivalent of n-butyl lithium, etc. must be additionally used to introduce dimethylphosphinyl group to the carboxylate compound of formula (E), a total of 3.0 to 4.5 equivalents of strong base such as n-butyl lithium must be used.

Fifthly, a diazo reaction should be carried out in ether solvent in order to obtain

the final compound of formula (F) from the carboxylic acid.

Lastly, since the method wholly included at least eight steps, it was complex and its yield was low, and the method included steps which were explosive and used toxic materials. Therefore, the method was not suitable for being used industrially and commercially.

Summary of the Invention

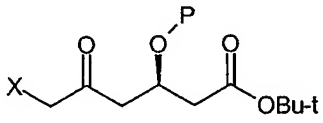
An object of the present invention is to provide a process for simply producing chiral intermediates which can be used for the preparation of HMG-CoA reductase inhibitors under mild conditions with high yields, without the above mentioned complex and dangerous steps.

Another object of the present invention is to provide new intermediates produced by the above process.

Further object of the present invention is to provide a process for the production of HMG-CoA reductase inhibitors using the above chiral intermediates.

Detailed Descriptions of the Invention

The present invention relates to the chiral compound of formula (I), process for the production thereof, and process for the production of HMG-CoA reductase inhibitors using the same.



(I)

wherein,

X is $P(=O)(R_1)_2$ or $S(O)R_1$, wherein R_1 is hydrogen, optionally substituted lower

alkyl of 1 to 4 carbon atoms, optionally substituted lower alkoxy of 1 to 4 carbon atoms, or optionally substituted aryl; and

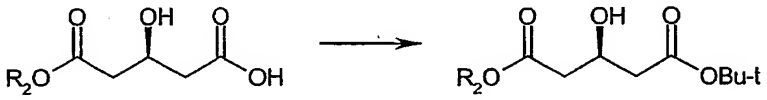
P is a hydroxy protecting group.

The present process for the production of the chiral compound of formula (I) comprises the steps of:

(i) selectively hydrolyzing the compound of formula (II) with a microorganism to give the compound of formula (III):

(II) (III)

(ii) reacting the compound of formula (III) with isobutylene under acidic catalyst to give the compound of formula (IV):

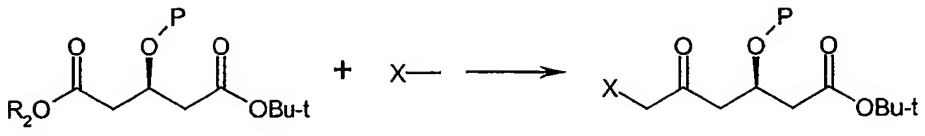


(III) (IV)

(iii) protecting the hydroxy group of the compound of formula (IV) to give the compound of formula (V):

(IV) (V)

(iv) reacting the compound of formula (V) with the compound of formula (VI) under base to give the compound of formula (I):



(V) (VI) (I)

wherein,

X is $P(=O)(R_1)_2$ or $S(O)R_1$, wherein R_1 is hydrogen, optionally substituted lower alkyl of 1 to 4 carbon atoms, optionally substituted lower alkoxy of 1 to 4 carbon atoms, or optionally substituted aryl;

R_2 is optionally substituted lower alkyl of 1 to 3 carbon atoms; and

P is a hydroxy protecting group, for example silyl group.

The present process for the production of the chiral compound of formula (I) is, hereinafter, described in detail.

Preparation of the compound of formula (III)

The compound of formula (III) is prepared from the compound of formula (II) by selective hyrolysis using a microorganism:

(II) (III)

wherein,

R_2 is optionally substituted lower alkyl of 1 to 3 carbon atoms.

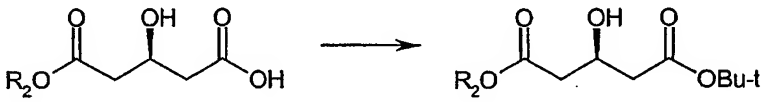
As the microorganism, lipase, protease, or esterase, etc. can be used, preferably with high substrate concentration of at least 10%.

The compound of formula (III) is prepared with high yield reaching 100% and high optical purity of about 99% starting from the compound of formula (II) which is a meso compound. Therefore, this step is very effective compared to the prior chemical

resolution which has the yield of about 50 to 80% and the optical purity of 95 to 98%.

Preparation of the compound of formula (IV)

The compound of formula (IV) is prepared by the addition reaction of the compound of formula (III) with isobutylene under acidic catalyst:



(III) (IV)

wherein,

R_2 is optionally substituted lower alkyl of 1 to 3 carbon atoms.

As the acidic catalyst, hydrochloric acid, sulfuric acid, nitric acid, acetic acid, trifluoroacetic acid, methanesulfonic acid, toluenesulfonic acid, trifluoromethanesulfonic acid, phosphoric acid, polyphosphoric acid, silica having impregnated metal such as titanium, or zeolite, etc. can be used. The acidic catalyst is preferably used in the amount of 0.000005~0.5 equivalents based on the compound of formula (III).

The addition reaction can be carried out in aromatic solvent such as benzene, toluene, and xylene, ether solvent such as tetrahydrofuran, dioxane, petroleum ether, diethyl ether, t-butylmethyl ether and dimethoxyethane, or halogen solvent such as dichloromethane, dichloroethane, chloroform, carbon tetrachloride, tetrachloroethylene, tetrachloroethane, chlorobenzene, dichlorobenzene, and trichlorobenzene, etc.

The reaction temperature is preferably less than 30°C, more preferably –30~10 °C. If the temperature is below -30 °C, the reaction rate slows down, and if the temperature is above 10 °C, isobutylene is vaporized so that an excessive amount of isobutylene should be used.

Preparation of the compound of formula (V)

The compound of formula (V) is prepared by protecting the hydroxy group of the compound of formula (IV):

(IV) (V)

wherein,

R2 is optionally substituted lower alkyl of 1 to 3 carbon atoms; and

P is a hydroxy protecting group, for example silyl group such as t-butyldimethylsilyl group.

If the hydroxy protecting group is a silyl group, for example t-butyldimethylsilyl group, the compound of formula (IV) is reacted with silyl halide, for example t-butyldimethylsilyl chloride in the presence of base.

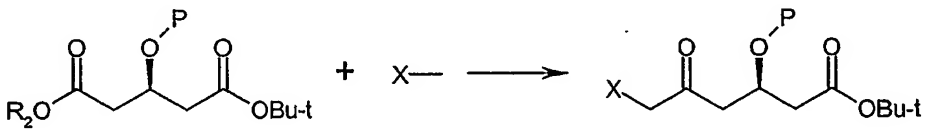
The reaction solvent includes aromatic solvent such as benzene, toluene, and xylene, and halogen solvent such as dichloromethane, dichloroethane, chloroform, carbon tetrachloride, tetrachloroethylene, tetrachloroethane, chlorobenzene, dichlorobenzene, and trichlorobenzene, etc.

The reaction temperature is preferably less than 60°C, more preferably 10~40 °C. If the temperature is below 10 °C, the reaction rate slows down, and if the temperature is above 40 °C, by-products occur.

As the base, amines such as trialkylamine, dialkylamine, alkylamine and imidazole, or inorganic compounds such as sodium hydroxide, potassium hydroxide, calcium hydroxide, sodium carbonate, potassium carbonate and calcium carbonate, etc. can be used, preferably in the amount of 1.0~10.0 equivalents based on the compound of formula (IV).

Preparation of the compound of formula (I)

The compound of formula (I), the target product, is prepared by reacting the compound of formula (V) with the compound of formula (VI) in the presence of base.



(V) (VI) (I)

wherein,

X is P(=O)(R1)2 or S(O)R1, wherein R1 is hydrogen, optionally substituted lower alkyl of 1 to 4 carbon atoms, optionally substituted lower alkoxy of 1 to 4 carbon atoms, or optionally substituted aryl;

R2 is optionally substituted lower alkyl of 1 to 3 carbon atoms; and

P is a hydroxy protecting group, for example silyl group.

As the base, alkali metal hydroxide, hydride, alkoxide, or alkyl, or alkaline earth metal hydroxide, hydride, alkoxide, or alkyl, or their mixtures, etc. can be used, preferably in the amount of 2.0~10.0 equivalents based on the compound of formula (V).

The reaction solvent includes ether solvent such as tetrahydrofuran, dioxane, petroleum ether, diethyl ether, t-butylmethyl ether and dimethoxyethane, and polar solvent such as dimethylformamide, dimethylacetamide, and hexamethylphosphoamide, etc.

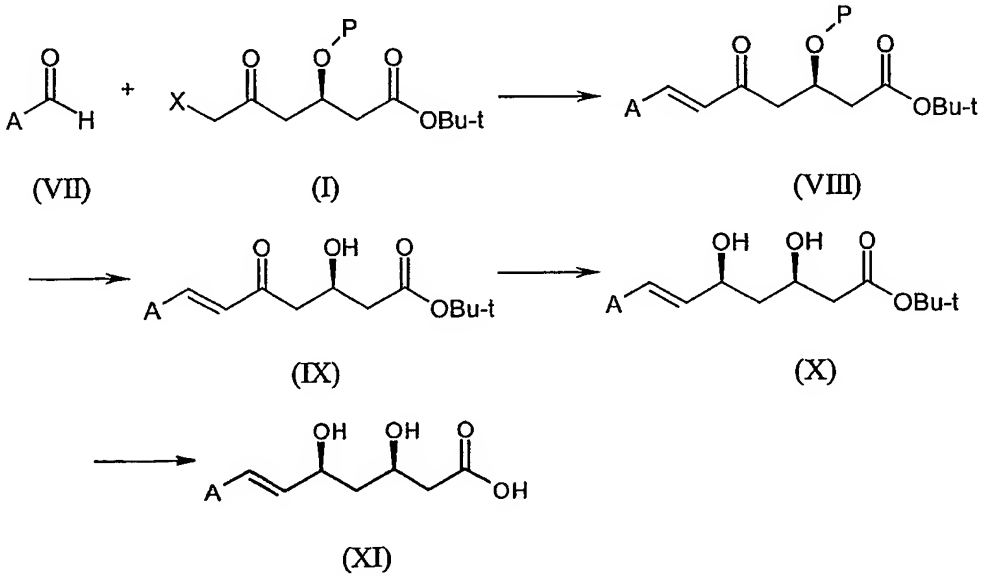
The reaction temperature is preferably less than 100°C, more preferably –78~40 °C. If the temperature is below -78 °C, the reaction rate slows down, and if the temperature is above 40 °C, side reactions proceed.

The compound of formula (VI) is preferably used in 2.0~10.0 equivalents based on the compound of formula (V).

The present invention introduced the step of preparing the compound of

formula (I) based on the fact that the nucleophilic substitution occurs selectively at the lower ester group of 1 to 3 carbon atoms among the lower ester group of 1 to 3 carbon atoms and t-butyl ester group. The above-mentioned Bristol-Myers Squibb's prior method imposed the selectivity by using the ester group and carboxylate group. In this case, the addition reaction occurred only at the ester group, but at least 1.0 equivalent of base was further required. However, the present invention can reduce the used amount of base by using two different ester groups.

The present chiral compound of formula (I) can be used as an intermediate for preparing various chiral medicaments, particularly HMG-CoA reductase inhibitors. For example, representative HMG-Co A reductase inhibitors, fluvastatin, rosuvastatin and pitavastatin of formula (XI) can be prepared, as shown in the below reaction scheme, by reacting the aldehyde compound of formula (VII) with the chiral compound of formula (I), deprotecting the hydroxy group of the trans compound of formula (VIII), reducing the ketone group of the compound of formula (IX), and cleaving the t-butyl group of the 1,3-dihydroxyester of formula (X).



(VII) (I) (VIII)

(IX) (X)

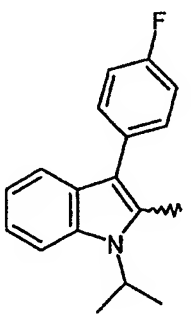
(XI)

wherein,

X is $P(=O)(R_1)_2$ or $S(O)R_1$, wherein R_1 is hydrogen, optionally substituted lower alkyl of 1 to 4 carbon atoms, optionally substituted lower alkoxy of 1 to 4 carbon atoms, or optionally substituted aryl;

P is a hydroxy protecting group; and

A is



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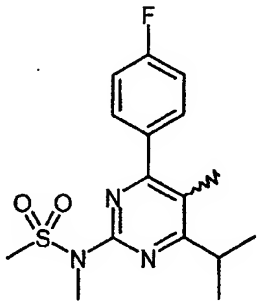

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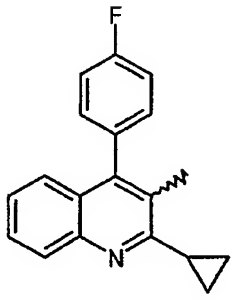

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The present process for the production of HMG-CoA reductase inhibitors is, hereinafter, described in detail referring to the above reaction scheme.

The condensation reaction of the aldehyde compound of formula (VII) with the chiral compound of formula (I) is carried out in the presence of base. As the base, alkali metal carbonate, hydroxide, hydride, alkoxide, or alkyl, or alkaline earth metal carbonate, hydroxide, hydride, alkoxide, or alkyl, etc. can be used. The base is preferably used in the amount of 1.0~5.0 equivalents based on the compound of formula (I), and the aldehyde is preferably used in the amount of 1.0~2.0 equivalents. The reaction solvent includes lower alcohol such as methanol, ethanol, and isopropanol, ether solvent such as tetrahydrofuran, dioxane, petroleum ether, diethyl ether, t-butylmethyl ether and dimethoxyethane, and polar solvent such as dimethylformamide, dimethylacetamide, hexamethylphosphoamide, and acetonitrile, etc.

If the protecting group is a silyl group, the deprotecting reaction of the hydroxy group of the trans compound of formula (VIII) can be simply carried out, in the presence of fluoride compound such as tetraalkylamonium fluoride and hydrofluoride in ether solvent such as tetrahydrofuran, dioxane, petroleum ether, diethyl ether, t-butylmethyl ether and dimethoxyethane, etc. The fluoride compound is preferably used in the amount of 1.0~5.0 equivalents based on the compound of formula (VIII).

The reduction of the ketone group of the compound of formula (IX) is carried out using alkali metal borohydride, cyanoborohydride, alkoxyborohydride, aluminiumhydride, alkylaluminiumhydride, or alkoxyaluminiumhydride, or alkaline earth metal borohydride, cyanoborohydride, alkoxyborohydride, aluminiumhydride, alkylaluminiumhydride, or alkoxyaluminiumhydride, etc. as a reducing agent. Also, in order to prepare syn-1,3-diol, a chelating agent such as trialkyborane, alkoxydialkylborane, dialkoxyalkylborane, and trialkoxyborane is used. The reducing agent and chelating agent are used preferably in the amount of 1.0~10.0 equivalents based on the compound of formula (IX). The reaction solvent includes ether solvent such as tetrahydrofuran, dioxane, petroleum ether, diethyl ether, t-butylmethyl ether and dimethoxyethane, etc.

The cleavage reaction of the t-butyl group of the 1,3-dihydroxyester of formula (X) is carried out preferably in the presence of acid, for example formic acid, acetic acid, trifluoroacetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, alkylsulfonic acid, and toluenesulfonic acid. The acid is used preferably in the amount of 0.001~100 equivalents based on the compound of formula (X). The reaction solvent includes organic acid such as formic acid and acetic acid, aromatic solvent such as benzene, toluene, and xylene, and halogen solvent such as dichloromethane, dichloroethane, chloroform, carbon tetrachloride, tetrachloroethylene, tetrachloroethane, chlorobenzene, dichlorobenzene, and trichlorobenzene, etc.

According to the present invention, new chiral intermediates which can be used for preparing chiral medicaments such as HMG-CoA reductase inhibitors can be simply prepared without dangerous reaction steps with high yields and high optical purity of at least 98%. Therefore, since chiral medicaments such as HMG-CoA reductase inhibitors can be produced economically with high purity via the chiral intermediates of the present invention, the process for the production of HMG-CoA reductase inhibitors using the chiral intermediates of the present invention does not have problem of removing by-products and disposing the waste, and therefore is suitable for being used industrially and commercially.

Examples

The following examples are intended to illustrate the present invention, however these examples are not to be construed to limit the scope of the invention.

Example 1:

Preparation of ethyl-(3S)-3-hydroxyglutaric acid

To 2,000ml of round-bottomed flask equipped with a stirrer and thermometer, 400.0g of diethyl-3-hydroxyglutaric acid and 400ml of water were added. Then, 20.0g of esterase(code number: CLS-BC-14011) was added and stirred at 37°C. After the reaction was completed, the esterase was separated using a filter paper, and 400ml of ethyl acetate was slowly added to the filtrate and stirred for 15 minutes. Then, aqueous phase and organic phase were separated, and the organic phase was distillated to give ethyl-(3S)-3-hydroxyglutaric acid(yield: 99.7%, purity: 98.0%, chiral purity: 99.5%).

Rf = 0.2(n-hexane/ethyl acetate, 1/1)

^{1}H NMR ($CDCl_3$, 200MHz) δ: 4.40~4.35(m, 1H); 4.10(q, 2H, J=7Hz); 3.45(bs, 1H); 2.50~2.41(d, 4H, J=6Hz); 1.26(t, 3H, J=7Hz).

Preparation of ethyl t-butyl-(3R)-3-hydroxyglutaric acid

To 2,000ml of round-bottomed flask equipped with a stirrer and thermometer, 211.3g of ethyl-(3S)-3-hydroxyglutaric acid and 400ml of dichloromethane were added. Afterwards, 67.3g of isobutylene gas and 12.8ml of sulfuric acid were added and stirred at -10°C. After the reaction was completed, 400ml of distilled water was slowly added and stirred for 15 minutes. Then, aqueous phase and organic phase were separated, and the organic phase was distillated under reduced pressure to give ethyl t-butyl-(3R)-3-hydroxyglutaric acid(distillation range: 115~116°C/2.0mmHg, yield: 74.5%, purity: 98.0%, chiral purity: 99.2%).

Rf = 0.8(n-hexane/ethyl acetate, 1/1)

^{1}H NMR ($CDCl_3$, 200MHz) δ: 4.41~4.36(m, 1H); 4.16(q, 2H, J=7Hz); 3.55(bs, 1H); 2.53~2.44(d, 4H, J=6Hz); 1.46(s, 9H); 1.27(t, 3H, J=7Hz).

Preparation of ethyl t-butyl-(3R)-3-(t-butyldimethylsilyloxy)glutaric acid

To 500ml of round-bottomed flask equipped with a stirrer and thermometer, 17.6g of ethyl t-butyl-(3R)-3-hydroxyglutaric acid and 100ml of dichloromethane were added. Afterwards, 6.2g of imidazole and 12.5g of t-butyldimethylsilyl chloride were added and stirred at room temperature. After the reaction was completed, 200ml of distilled water was added and stirred for 15 minutes. Then, aqueous phase and organic phase were separated, and the organic phase was distillated. The resulting residue was subjected to silica gel column chromatography(eluent: n-hexane/ethyl acetate, 4/1) to give ethyl t-butyl-(3R)-3-(t-butyldimethylsilyloxy)glutaric acid(yield: 94.8%, purity: 99.0%, chiral purity: 99.0%).

Rf = 0.8(n-hexane/ethyl acetate, 2/1)

^{1}H NMR ($CDCl_3$, 200MHz) δ: 4.54~4.36(m, 1H); 4.12(q, 2H, J=6Hz); 2.55 ~

2.44(dd, 4H, J=6Hz, J=2Hz); 1.45(s, 9H); 1.25(t, 3H, J=7Hz); 0.85(s, 9H); 0.06(s, 6H).

Preparation of t-butyl (3R)-3-(t-butyldimethylsilyloxy)-6-dimethoxyphophinyl-5-oxohexanate

To 1,000ml of round-bottomed flask equipped with a stirrer and thermometer, 17.8g of dimethyl methylphosphonate and 150ml of tetrahydrofuran were added under nitrogen atmosphere. Afterwards, 82.5ml of 1.6M n-butyllithium in n-hexane was slowly added for 15 minutes and stirred for 1 hour at -78°C, and 19.1g of ethyl t-butyl-(3R)-3-(t-butyldimethylsilyloxy)glutaric acid was added and stirred. After the reaction was completed, 200g of 5% HCl aqueous solution and 400ml of ethyl acetate were added and stirred for 15 minutes. Then, aqueous phase and organic phase were separated, and the organic phase was distillated. The resulting residue was subjected to silica gel column chromatography(eluent: n-hexane/ethyl acetate, 1/1) to give t-butyl (3R)-3-(t-butyldimethylsilyloxy)-6-dimethoxyphophinyl-5-oxohexanate(yield: 77.6%, purity: 99.5%, chiral purity: 99.1%).

Rf = 0.3(n-hexane/ethyl acetate, 1/1)

^{1}H NMR ($CDCl_3$, 200MHz) δ: 4.54~4.45(m, 1H); 3.76(d, 6H, J=11Hz); 3.10(d, 2H, J=23Hz); 2.85(d, 2H, J=6Hz); 2.39(d, 2H, J=6Hz); 1.42(s, 9H), 0.83(s, 9H), 0.06(d, 6H, J=5Hz).

Example 2:

Preparation of t-butyl 7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidine-5-yl]-(3R)-3-(t-butyldimethylsilyloxy)-5-oxo-6-heptenate

To 500ml of round-bottomed flask equipped with a stirrer and thermometer, 4.15g of potassium carbonate and 50ml of isopropanol were added at room temperature under nitrogen atmosphere. Afterwards, 4.24g of t-butyl (3R)-3-(t-

butyldimethylsilyloxy)-6-dimethoxyphophinyl-5-oxohexanate prepared in Example 1 was added at room temperature under nitrogen atmosphere and stirred for 1 hour, and then 3.24g of 4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-5-pyrimidinecarbaldehyde was added at room temperature under nitrogen atmosphere and stirred. After the reaction was completed, the solvent was removed by distillation under reduced pressure, and 100g of 10% HCl aqueous solution and 100ml of ethyl acetate were added and stirred for 15 minutes. Then, aqueous phase and organic phase were separated, and the organic phase was distillated to give t-butyl 7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidine-5-yl]-(3R)-3-(t-butyldimethylsilyloxy)-5-oxo-6-heptenate.

Rf = 0.4(n-hexane/ethyl acetate, 7/1)

Preparation of t-butyl 7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidine-5-yl]-(3R)-3-hydroxy-5-oxo-6-heptenate

The compound obtained in the above step was added to 250ml of round-bottomed flask equipped with a stirrer and thermometer without purification, and 20ml of tetrahydrofuran and 12ml of 1.0M tetrabutylammonium fluoride in tetrahydrofuran were added under nitrogen atmosphere and stirred at room temperature. After the reaction was completed, 100g of 10% sodium carbonate solution and 100ml of ethyl acetate were added and stirred for 15 minutes. Then, aqueous phase and organic phase were separated, and the organic phase was distillated. The resulting residue was subjected to silica gel column chromatography(eluent: n-hexane/ethyl acetate, 1/1) to give t-butyl 7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidine-5-yl]-(3R)-3-hydroxy-5-oxo-6-heptenate(yield: 76.6%).

Preparation of t-butyl 7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidine-5-yl]-(3R,5S)-3,5-dihydroxy-6-heptenate

4.97g of the compound obtained in the above step was added to 100ml of round-bottomed flask equipped with a stirrer and thermometer, and 20ml of tetrahydrofuran and 5ml of methanol were added under nitrogen atmosphere and stirred at room temperature. Afterwards, 13.3ml of 1.0M triethylborane in tetrahydrofuran was slowly added for 15 minutes and stirred for 0.5 hours at -78°C, and then 0.42g of sodium borohydride was added and stirred. After the reaction was completed, 14ml of acetic acid was added and stirred for 0.5 hours, and then 200g of 10% sodium carbonate solution and 200ml of ethyl acetate were added. Then, aqueous phase and organic phase were separated, and the organic phase was distillated. Afterwards, 20ml of methanol was added to the resulting residue, stirred for 15 minutes at room temperature, and concentrated, 5 times repeatedly. The resulting residue was subjected to silica gel column chromatography(eluent: dichloromethane/ethyl acetate, 3/1) to give t-butyl 7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidine-5-yl]-(3R,5S)-3,5-dihydroxy-6-heptenate(yield: 90.6%).

Rf = 0.3(dichloromethane/ethyl acetate, 3/1)

Preparation of rosuvastatin sodium salt

2.35g of the compound obtained in the above step was added to 100ml of round-bottomed flask equipped with a stirrer and thermometer, and 10ml of formic acid was added and stirred at room temperature. After the reaction was completed, the reactants were concentrated, and 40ml of ethanol and 50ml of 0.1N sodium hydroxide solution were added and stirred for 10 minutes at room temperature. Then, the reactants were concentrated, and 20ml of ethanol was added and stirred for 10 minutes, 5 times repeatedly. Afterwards, 50ml of ether was added to the resulting residue, and stirred for 1 hour at room temperature. The resulting white crystals were filtered through a filter paper, washed with 10ml of ether three times, and dried to give

rosuvastatin sodium salt(yield: 89.7%).

^{1}H NMR ($CDCl_3$, 200MHz) δ: 7.15(m, 4H); 6.62(d, 1H, J=16Hz); 4.99(dd, 1H, J=16Hz, 7Hz); 4.22(m, 1H), 3.72(m, 2H); 3.36(s, 3H); 2.24(m, 2H); 2.13(s, 3H); 1.37(s, 3H); 1.34(s, 3H)

$[\alpha]_D$ = +29.0(C=1.0, distilled water).

What is claimed is:

1. A process for the production of the chiral compound of formula (I) comprising the steps of:

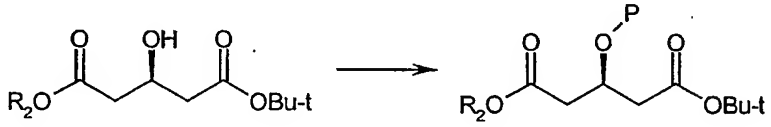
(i) selectively hydrolyzing the compound of formula (II) with a microorganism to give the compound of formula (III):

(II) (III)

(ii) reacting the compound of formula (III) with isobutylene under acidic catalyst to give the compound of formula (IV):

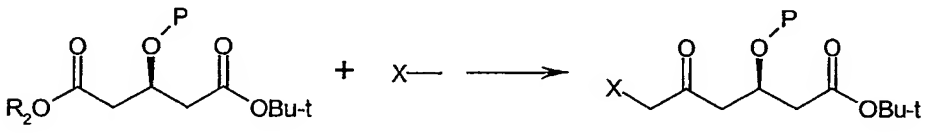
(III) (IV)

(iii) protecting the hydroxy group of the compound of formula (IV) to give the compound of formula (V):



(IV) (V)

(iv) reacting the compound of formula (V) with the compound of formula (VI) to give the compound of formula (I):



(V) (VI) (I)

wherein,

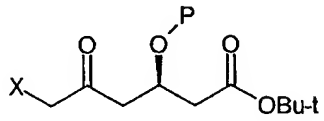
X is $P(=O)(R_1)_2$ or $S(O)R_1$, wherein R_1 is hydrogen, optionally substituted lower alkyl of 1 to 4 carbon atoms, optionally substituted lower alkoxy of 1 to 4 carbon atoms, or optionally substituted aryl;

R_2 is optionally substituted lower alkyl of 1 to 3 carbon atoms; and

P is a hydroxy protecting group.

2. The process according to claim 1, wherein X is $P(=O)(OMe)_2$, and P is t-butyldimethylsilyl group.

3. A chiral compound of formula (I):



(I)

wherein,

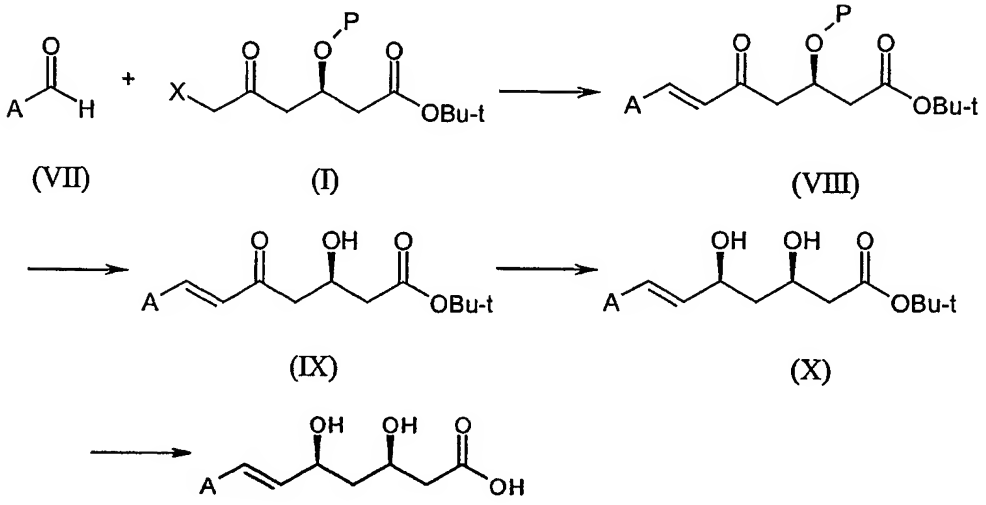
X is $P(=O)(R_1)_2$ or $S(O)R_1$, wherein R_1 is hydrogen, optionally substituted lower alkyl of 1 to 4 carbon atoms, optionally substituted lower alkoxy of 1 to 4 carbon atoms, or optionally substituted aryl; and

P is a hydroxy protecting group.

4. The chiral compound according to claim 3, wherein X is $P(=O)(OMe)_2$, and P is t-butyldimethylsilyl group.

5. A process for the production of the HMG-CoA reductase inhibitor of formula (XI) comprising the steps of reacting the aldehyde compound of formula (VII) with the chiral compound of formula (I), deprotecting the hydroxy group of the trans compound of formula (VIII), reducing the ketone group of the compound of formula (IX), and

cleaving the t-butyl group of the 1,3-dihydroxyester of formula (X):



(VII) (I) (VIII)

(IX) (X)

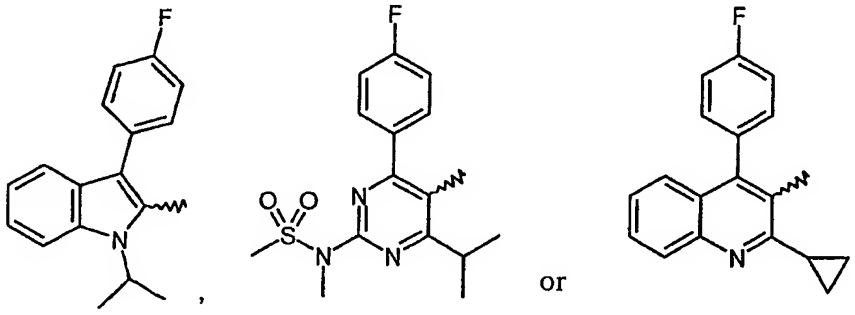
(XI)

wherein,

X is $P(=O)(R_1)_2$ or $S(O)R_1$, wherein R_1 is hydrogen, optionally substituted lower alkyl of 1 to 4 carbon atoms, optionally substituted lower alkoxy of 1 to 4 carbon atoms, or optionally substituted aryl;

P is a hydroxy protecting group; and

A is



or

6. The process according to claim 5, wherein the HMG-CoA reductase inhibitor is rosuvastatin.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR03/00707

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C07F 9/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC7 C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
KR, JP: IPC as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y		1-2
X	EP 554455 A1 (SHIONOGI SEIYAKU KABUSHIKI KAISHA) 11 AUGUST 1993 See the whole document	3-4
X	Terry Rosen et al., 'A Convenient Assay for the Optical Purity of MOnomethyl 3-Hydroxypentanedioate', J. Org. Chem. 1984, 49(19), 3657-3659 See the whole document	3-4
Y		1-2
A	Toshiro Konoike et al., 'Practical Synthesis of Chiral Synthons for the Preparation of HMG-CoA Reductase Inhibotors', J. Org. Chem., 1994, 59(25), 7849-7854 See the whole document	1-6
A	US 4804770 A (E.R.Squibb & Sons, Inc) 14 FEBRUARY 1989 See the whole document	1-6

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 JULY 2003 (14.07.2003)	15 JULY 2003 (15.07.2003)

Name and mailing address of the ISA/KR	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR03/00707

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